1-11-05

AF/1617 IFW

Attorney Docket No.: 6225.200-US

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Koch et al

Serial No.: 10/016,858 Group Art Unit: 1617

Filed: December 14, 2001 Examiner: Hui, San Ming R.

For: Hormone Composition

CERTIFICATE OF MAILING UNDER 37 CFR 1.8(a)

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

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APPEAL BRIEF

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REAL PARTY IN INTEREST

The Real Party-In-Interest is Novo Nordisk A/S, the assignee of record.

RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

STATUS OF THE CLAIMS

The claims which are subject to this appeal are claims 35, 36, 40, 43, 45-47 and 49-53. Of the filed claims, all other claims, namely claims 1-34, 37-39, 41, 42, 44, and 48, have been cancelled. The text of the claims subject to this appeal is set forth in the Claims Appendix.

STATUS OF AMENDMENTS

No amendments have been requested following final rejection.

SUMMARY OF THE SUBJECT MATTER OF THE CLAIMS

Two independent claims, claims 35 and 40, are among the claims subject to this appeal. Both relate to methods of treating atrophic vaginitis, which is a condition that can occur in postmenopausal women and is associated with estrogen deficiency (in the specification at page 12, lines 25-29).[1] The presently claimed invention involves administering, vaginally (in the specification at page 1 lines 2-3),[2] in tablet form (in the specification at page 4 lines 3-5),[3] a lower dose of estrogen than that administered by the prior art, which typically is one 25 μg estradiol-containing, vaginally-administered tablet "daily for the first two weeks of treatment and, thereafter, one tablet twice a week" (in the specification at page 1 lines 13-14).[4]

Specifically, according to independent claim 35, a tablet containing about 10 μg estradiol (the specification at page 20 line 23 through page 21 line 14)[5] is administered vaginally once (in the specification at page 3 lines 13-15)[6] or twice (in the specification at page 3 lines 23-24)[7] per week. According to independent claim 40, a tablet containing about 5 μg estradiol is administered vaginally twice weekly (in the specification at page 3 lines 21-23)[8].

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1 "As endogenous estrogen production declines during menopause, the vagina and other estrogen-dependent tissues gradually undergo atrophic changes. The loss of estrogen-influenced cellular maturation results in a condition identified as atrophic vaginitis. The symptoms of atrophic vaginitis include dryness, soreness, irritation, and dyspareunia. Additionally, the vaginal epithelium becomes more susceptible to infection and secondary inflammation."

2 "The present invention relates to a composition containing oestrogen, which is to be administered vaginally."

3 "According to a further preferred embodiment, this invention relates to the use wherein administration is performed using a tablet."

4 "A usual treatment is one tablet of Vagifem containing 25 μg estradiol daily for the first 2 weeks of treatment and, thereafter, one tablet twice a week."

5 Example 4 discloses the manufacture of a 10 μg estradiol-containing tablet.

6 "The present invention relates to use of an oestrogen in the manufacture of a composition containing estrogen for the treatment of atrophic vaginitis in a woman, by administering weekly an amount of about 10 to about 30 μg estradiol to a woman." *see also* Example 4 at pages 20-21, which describes the manufacture of a 10 μg estradiol-containing tablet.

7 "According to a further preferred embodiment, this invention relates to the use wherein twice weekly about 9 to about 11 μg estradiol is administered;" *see also* Example 1 at page 5 lines 6-13, in which subjects were treated with 10 μg estradiol-containing tablets administered vaginally twice weekly.

8 "According to a further preferred embodiment, this invention relates to the use wherein twice weekly about 5 to about 15 μg estradiol is administered."

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Claims 35, 36, 40, 43, 45-47, and 49-53 are rejected under 35 U.S.C. §103(a) as obvious over United States Patent No. 6,060,077 by Meignant ("Meignant") in view of Mettler and Olsen, 1991, Maturitas 14:23-31 ("Mettler") and "the Vagifem monograph," Novo Nordisk, 2000.

Meignant is cited as teaching administering low dose 17-β-estradiol in a dosage of, for example, 2.5 or 5 μg, locally to treat atrophic vaginitis with an aim to avoid systemic absorption of estrogen. The Examiner acknowledges that Meignant neither expressly teaches tablets having the specific formulations disclosed in the instant specification nor weekly or bi-weekly administration.

Mettler is cited as teaching atrophic vaginitis by vaginal administration of the Vagifem® tablet, which contains 25 μg estradiol and is administered once or twice a week.

The Vagifem monograph is cited as teaching that the Vagifem® tablet has a formulation that shares components with specific embodiments of the presently claimed invention, such as hypromellose, lactose monohydrate, maize starch and magnesium stearate, and has a film coating which contains hypromellose and polyethylene glycol.

The Examiner contends:

> Possessing the teachings of the cited prior art, one of ordinary skill in the art would have reasonably expected to employ a Vagifem tablet, in a lower dose to avoid systemic side effects, in a method of treating atrophic vaginitis[9]

and

> One of ordinary skill in the art would have been motivated to adjust the dosage frequency to the herein claimed dosage frequency. The optimization of result effect parameters (e.g. dosage range, dosing regimens to avoid side effects) is obvious as being within the skill of the artisan.[10]

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9 Final Rejection dated May 17, 2004, page 4.

10 *Id.*

ARGUMENT

Appellants assert that the claimed invention is not obvious, because the cited references, taken singly or in combination, do not suggest or create any reasonable expectation that a low dose (5 or 10 μg estradiol) tablet administered vaginally once (for the 10 μg tablet) or twice a week, could successfully treat atrophic vaginitis. In short, this is because Meignant, while teaching low dose formulations of estradiol, discloses a higher weekly dosage and teaches against the use of a tablet, taking the position that tablets preclude the use of low dose estrogen. As such, in view of Meignant, taken alone or together with Mettler or the Vagifem® monograph, the skilled artisan would not have expected that delivery of a low weekly dose of estrogen via a vaginal tablet would or could provide therapeutic benefits. Appellants have presented not only argument asserting this position, but have also submitted a declaration by an expert in hormone replacement therapy averring that the skilled practitioner would not, in view of the cited references or general experience, have expected the claimed method to be clinically effective.

Appellants invite the Board's attention to the following text from Meignant, which characterizes higher dose vaginal tablets as prior art to its purported invention (Meignant at column 1 lines 46-65, *emphasis added*):

> A galenical formulation comprising 17β-estradiol in the form of vaginal tablets which are administered daily has also been proposed for such local treatment. Such tablets contain a matrix comprising an excipient such as a cellulosic polymer which absorbs traces of residual vaginal moisture to impregnate the matrix containing the active principle and gradually release the latter.
>
> *However, because of their particular galenical form, the dosage of such tablets must be relatively high to obtain the desired results, typically a dosage of 25 micrograms (μg) of 17β-estradiol per tablet* (one tablet corresponds to one unit dose) to provide the desired cytological, histological and clinical improvement in the vaginal mucous membrane. Because of this relatively high dose, endometrial proliferation was noted in certain patients during clinical studies, indicating systemic passage of 17β-estradiol: see in particular C. Fielding et al., "Preoperative Treatment with Estradiol in Women Scheduled for Vaginal Operation for Genital Prolapse. A Randomised, Double-Blind Trial", Maturitas, 1992, 15, 241-249.

Meignant distinguishes its formulations from vaginal tablets as follows (Meignant at column 1 line 66 through column 2 line 12, *emphasis added*):

> One aim of the present invention is to propose a medicament of the above type *with a particular galenical formulation which enables the dosage of 17β-estradiol to be reduced* so as to avoid systemic passage despite the extreme sensitivity of the vaginal mucous membrane to estrogens, while ensuring satisfactory trophic effectiveness. *According to the invention, this medicament is characterized by a unit galenical formulation comprising a natural estrogen selected from 17β-estradiol and its salts in solution or in suspension in a lipophilic agent*, with an estrogen content which corresponds to an equivalent unit dose of at most 15 μg, preferably less than 10 μg, of 17β-estradiol, a hydrophilic gel-forming bioadhesive agent, a gelling agent for the lipophilic agent and a hydrodispersible agent.

Thus, Meignant teaches that low dose estrogen (estradiol, in particular) cannot achieve therapeutic levels if administered in tablet form, but rather must be administered in solution or suspension with a lipophilic agent. To accommodate the estrogen-containing solution or suspension, Meignant teaches dosage formulations comprised in hard or soft capsules or in suppositories (notably, *not tablets*).

Reciprocally, the instant specification distinguishes the tablets of the claimed invention from the formulations of Meignant (at page 1 line 22 through page 2 line 3, *emphasis added*):

> A pharmaceutical medicament for local, essentially non-systemic, treatment of vaginal dryness, in particular in the menopausal woman, characterized by a unit galenical formulation comprising a natural estrogen selected from the group consisting of 17β-estradiol and its salts and its derivatives in solution or in suspension in a lipophilic agent, with an estrogen content which corresponds to an equivalent unit dose of at most 15 μg, preferably less than 10 μg, of 17β-estradiol, a hydrophilic gel-forming bioadhesive agent, a gelling agent for the lipophilic agent, and a hydrodispersible agent, is described in US patent specification No. 6,060,077 [*Meignant*]. Hence, according to the 6,060,077 specification, 17β-estradiol and its salts and its derivatives are in solution or in suspension. *Consequently, it cannot be a tablet.*

Thus, the estrogen-containing solutions and suspensions of Meignant cannot be comprised in a tablet, according to the usage of the word "tablet" in both the instant specification as well as Meignant.

Moreover, Meignant teaches a higher weekly dose than that presently claimed. As regards a 10 μg estradiol-containing lipophilic solution or suspension, Meignant teaches the following dosing regimen (Meignant at column 4 lines 20-25):

> The dosage must be selected so as to relieve local problems and prevent transvaginal absorption to a maximum extent. These aims are achieved by selecting a dose of 10 μg of 17β-estradiol, corresponding to a unit dose (a single daily administration, or less frequently still).

Meignant's recommended dosage of 70 μg per week or less cannot be considered to render obvious the much lower weekly doses of the presently claimed invention.

Similarly, Mettler teaches against the low doses presently claimed. Mettler compares twice-weekly administration of 25 μg estradiol (administered as a Vagifem® tablet) with once-weekly treatment and concludes (at page 30, second full paragraph), " . . . twice-weekly administration of 25 μg [17β- *estradiol*] is the lowest effective dose for the long-term treatment of post-menopausal oestrogen-deficiency-derived atrophic vaginitis" and again (at page 30, fifth full paragraph) "[t]wice-weekly administration of 25 μg [17β-*estradiol*] seems to be the lowest effective dose for the successful treatment of such symptoms."

Accordingly, Appellants assert that the skilled artisan, armed with Meignant's teaching that the effectiveness of low dose estrogen therapy can only be achieved if the estrogen is in solution or suspension in a lipophilic agent, and that this requirement is not and cannot be achieved by a tablet, would have no reason whatsoever, in view of *tablet*-directed Mettler and/or the Vagifem® monograph, to reach the conclusion that a low-dose estrogen *tablet*, administered according to the present claims, would be therapeutically successful. Particularly in view of Meignant's recommendation, that the estrogen suspension/solution be administered at a weekly dose much higher (70 μg or less) than that of the present invention, and Mettler's teaching that the lowest effective tablet dosing administers 25 μg estradiol twice a week, the skilled artisan would expect the presently claimed treatment regimens to be therapeutic failures, and would be surprised to learn that a regimen utilizing a low-dose estrogen tablet could be effective.

As further evidence of the non-obviousness of the present invention, Appellants invite the Board's attention to Santen et al., 2002, Menopause 9:179 ("Santen"; Exhibit A) and the Declaration Under 37 C.F.R. §1.132 of Dr. Lila E. Nachtigall (the "Nachtigall Declaration"; Exhibit B), both of which were submitted to the Patent Office in the Response filed February 25, 2004. These references demonstrate that even after the present application was filed, and despite access to Meignant (which issued May 9, 2000), persons skilled in the art would not have expected that low-dose treatment as claimed would provide therapeutic benefits.

Santen, which is not prior art against the present claims, reports the results of a study in which a vaginal cream containing 10 μg estradiol/dose was administered daily for three weeks and then twice-weekly for an extended period. Notably, the article states (at page 180, first column, last paragraph, emphasis added):

> The lowest dose of vaginal E2 [*estradiol*] reported to be effective for treating vaginal atrophy is 5-10 μg/*day*, delivered via a silastic ring. The next lowest effective dose is a *daily* 10-μg vaginal tablet.

Dr. Lila E. Nachtigall is, as evidenced by her *curriculum vitae*, an internationally recognized expert in the field of hormone replacement therapy who maintains an extensive clinical practice and thus is well-positioned to evaluate the beliefs of those of ordinary skill in the art at the time the present application was filed.

Dr. Nachtigall states that, in her opinion, nothing in the prior art -- or in the clinical experience of practitioners in the hormone replacement therapy field -- would have suggested that once or twice weekly administration of a tablet containing 10 μg estradiol would be useful to treat atrophic vaginitis (Nachtigall Declaration, at ¶3). Dr. Nachtigall also points out specifically that (i) Meignant does not provide any basis for asserting a clinical benefit for low-dose estradiol administration via a tablet (Nachtigall Declaration at ¶4); (ii) Meignant's assertion of superiority for soft capsules over tablets is misplaced (Nachtigall Declaration at ¶5); and (iii) even the positive experience of medical practitioners with the present Vagifem® product (25 μg estradiol) would not have supported a reasonable expectation of success with lower doses of estradiol as presently claimed (Nachtigall Declaration at ¶6). To this last point, Dr. Nachtigall states (Nachtigall Declaration at ¶6):

> Furthermore, our extensive experience with the current Vagifem® product (as reflected, e.g., in the Mettler et al. article and in the Vagifem® monograph) cannot be extrapolated to the use of a much lower dosage regimen as in the present invention. It was quite surprising that Vagifem® could provide clinical benefit; and -- in view of the absence of anything in the medical literature (or in anecdotal clinical experience, for that matter) that would have suggested that *further* lowering of the dosage by 40% or 80% would still provide enough estradiol locally to result in improvement of symptoms -- the invention described and claimed in the present application was even more surprising.

It is important to add that, although unexpected, the present invention is, in fact, therapeutically successful. In this regard, the Board's attention is invited to Examples 1-3 at pages 5-20 of the instant specification, and Figures 1-13. These Examples report the results of studies performed in human patients, in which post-menopausal women were treated with vaginally-administered tablets containing 10 or 25 μg 17β-estradiol, in a regimen of once-a-day for two (2) weeks, and then twice weekly for ten (10) weeks thereafter. Example 3 reports the results of a phase III, multicenter, randomized, double blind, placebo-controlled parallel group study conducted in nine centers in the United States (the instant specification at page 13 lines 10-11). 230 post-menopausal women were involved in the study (in the instant specification at page 12 lines 3-4). It was found that "treatment with 25 or 10 μg [17β-*estradiol*] resulted in comparable improvements as assessed by both patients and investigators" (the instant specification at page 17 lines 27-28) and (the instant specification at page 12 lines 21-23):

> Both the 25 and 10 μg [17β-*estradiol*] vaginal tablets provided relief of vaginal symptoms, improved vaginal health, and increased maturation of both the vaginal and urethral mucosa without abnormal endometrial growth.

Accordingly, Appellants have proven, in human clinical trials, that the presently claimed invention is therapeutically successful, despite the doubts and countervailing teachings expressed in the Nachtigall Declaration and the prior art.

According to *Graham v. John Deere Co.,* 383 U.S. 1, 148 U.S.P.Q. 459 (1966), any assessment of obviousness must consider (i) the scope and contents of the prior art; (ii) the differences between the prior art and the claims at issue; (iii) the level of ordinary skill in the

pertinent art; and (iv) objective evidence of non-obviousness. In the case at hand, the prior art teaches against the use of the claimed low weekly doses of estradiol, administered via vaginal tablet(s). As to consideration of objective evidence of non-obviousness, not only does data presented in the application support the unexpected success of the present invention, but Appellants have provided additional evidence, in the form of the Santen reference and the Nachtigall Declaration, which illustrates the skepticism of skilled artisans or, in the case of Dr. Nachtigall, an expert, that the claimed invention would be therapeutically useful. "Expressions of disbelief by experts constitute strong evidence of nonobviousness." *Environmental Designs, Ltd. v. Union Oil Co. of Cal.*, 713 F.2d 693, 698, 218 USPQ 865, 869 (Fed. Cir. 1983) (citing *United States v. Adams*, 383 U.S. 39, 52, 148 USPQ 479, 483-484 (1966)), and *see also In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988);*Burlington Industries Inc. v. Quigg*, 822 F.2d 1581, 3 USPQ2d 1436 (Fed. Cir. 1987); and *Gillette Co. v. S.C. Johnson & Son* , 919 F.2d 720, 726, 16 USPQ2d 1923, 1928 (Fed. Cir. 1990).

Appellants assert that the Examiner has not assigned adequate evidentiary weight to either Santen or the Nachtigall Declaration, and has peremptorily refuted their teachings by merely restating what is disclosed in the cited art. In particular, in the Final Official Action dated May 17, 2004, the Examiner states:

> Applicant's arguments in paragraph 6[11], declaration by Dr. Nachtigall averring unexpected success of employing the herein claimed low dose of estradiol have been considered, but are not found persuasive. As discussed above, Meignant clearly discloses 2.5-15 μg of estradiol, which encompassed the herein claimed dosage, as effective in treating vaginitis. There is no data as to comparing the dosage forms of Meignant and that of the instant invention to demonstrate unexpected benefits of employing the herein claimed dosage forms. Therefore, absent evidence to the contrary, possessing the teachings of the cited prior art, one of ordinary skill in the art would have reasonably expected to employ the herein claimed estradiol regimen to treat atrophic vaginitis.

This line of reasoning focuses on Meignant, and does not appreciate that paragraph 6 of the Nachtigall Declaration has conceptually moved beyond that reference. Dr. Nachtigall, in paragraphs 3-5 of her Declaration, explains why she finds the prophetic disclosure of Meignant inapposite and untenable. In paragraph 6, Dr. Nachtigall compares prior art use of β-estradiol tablets (rather than the lipophilic suspensions and solutions of Meignant) with the present

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[11] Quoted *supra*.

invention, and explains that *even as regards β-estradiol-containing tablets* "the invention described and claimed in the present application was even more surprising."

In view of the foregoing arguments, and in particular (i) the fact that Meignant, the primary reference cited against the claims, teaches away from the claimed invention; (ii) the lack of awareness in the art, subsequent to the filing date of the application and despite the accessibility of practitioners to Meignant, that low-dose vaginal tablets could be effective in treating atrophic vaginitis; (iii) the fact that the lowest effective weekly dosages envisaged by the art are higher than those claimed; (iv) the surprise evinced by an *expert* practitioner that the claimed formulations are effective, and (v) the unexpected success of the claimed invention, Appellants request that the obviousness rejection be withdrawn and that the claims under appeal be allowed to issue.

Respectfully submitted,

Date: January 7, 2005

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23650

CLAIMS APPENDIX

The status of all claims is as follows:

1-34. Cancelled.

35. (Rejected) A method for treating atrophic vaginitis in a patient in need of such treatment, said method comprising administering vaginally to said patient an amount of about 10 μg estradiol, wherein administration of said amount occurs once or twice per week and wherein said estradiol is administered in tablet form.

36. (Rejected) A method according to claim 35, wherein the patient is a menopausal or post-menopausal woman.

37-39. Cancelled.

40. (Rejected) A method for treating atrophic vaginitis in a patient in need of such treatment, said method comprising administering vaginally to said patient an amount of about 5 μg estradiol, wherein administration of said amount occurs twice weekly and wherein said estradiol is administered in tablet form.

41-42. Cancelled.

43. (Rejected) A method according to claim 35, wherein no progestogen is administered.

44. (Cancelled)

45. (Rejected) A method according to claim 35, wherein said at least once-weekly administration occurs over a time period of more than two weeks.

46. (Rejected) A method according to claim 45, wherein said period of time is more than 1 month.

47. (Rejected) A method according to claim 46, wherein said period of time is more than 3 months.

48. Cancelled.

49. (Rejected) A method according to claim 35, wherein each tablet comprises, in addition to estradiol or a therapeutically equivalent amount of a salt thereof, about 53.7 mg hypromellose, about 17.9 mg lactose monohydrate, about 8 mg maize starch, about 0.4 mg magnesium stearate.

50. (Rejected) A method according to claim 35, wherein each tablet is coated with a film consisting of about 0.5 mg hypromellose and about 0.06 mg macrogel 6000 (polyethylene glycol 6000 NF).

51. (Rejected) A method according to claim 35, wherein there is undetectable systemic absorption of said estradiol following said administration.

52. (Rejected) A method according to claim 35, wherein said treatment results in a vaginal pH value below bout 5.5.

53. (Rejected) A method according to claim 35, wherein said treatment results in one or more of: Relief of vaginal symptoms, improved urogenital atrophy, decreased vaginal pH, and improved cytologic maturation of the vaginal and/or urethral mucosa.

EVIDENCE APPENDIX

Santen et al., 2002, Menopause 9:179 ("Santen"; Exhibit A)

Declaration Under 37 C.F.R. §1.132 of Dr. Lila E. Nachtigall (the "Nachtigall Declaration"; Exhibit B)

Both submitted to the Patent Office in the Response filed February 25, 2004.

RELATED PROCEEDINGS APPENDIX

There are no related appeals or interferences.